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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,822	03/19/2004	Lawrence W. Stanton	135/003P	7106

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,822	STANTON ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-28* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-21-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-21-08 has been entered.

Claims 21-28 are pending. Claims 21 and 24-28 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of

ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 21 and 24-28 are directed to a method for assessing a culture comprising human embryonic stem cells for the presence of undifferentiated cells by measuring PODXL expression level in the culture under a first set of conditions and a second set of conditions, wherein the second set of conditions contains an agent suitable for inducing differentiation of the human embryonic stem cells and the first set of conditions does not have said agent, and a decrease in PODXL level under second set of conditions relative to that of first set of conditions indicates there are more undifferentiated cells in the culture under first set of conditions. Claims 24 and 25 specify the PODXL expression level is measured at the protein level and by antibody assay, respectively. Claim 26 specifies the PODXL expression level is measured using flow cytometry. Claims 27 and 28 specify the first set of conditions comprises culturing the cells in the presence of a feeder layer or a matrix.

The specification discloses a plurality of marker genes that appear to be more abundantly expressed in undifferentiated hES cell lines when compared to that in differentiated hES cell

lines (i.e. differentiated hES cell lines that have been induced to differentiate to embryoid body (EB) formation, exposure to retinoid acid to differentiate to neuronal precursor cells, and exposure to DMSO to differentiate to hepatocyte precursor cells). The specification discloses a plurality of marker genes that appear to be less abundantly expressed in undifferentiated hES cell lines as compared to that in differentiated hES cell lines (Examples 1-3, Table 2 and 3). Examples 4, 5 and 8 demonstrate high level expression of PODXL in undifferentiated hES cells and PODXL expression level decreased after growing the undifferentiated hES cells in unconditioned culture medium by real-time PCR assay (mRNA level).

The claims encompass assessing a culture comprising human embryonic stem cells for the presence of undifferentiated cells by measuring PODXL protein expression level in the culture at two different sets of culture conditions. The specification fails to provide adequate guidance and evidence for how to assess the presence of undifferentiated hES cells by measuring PODXL protein expression level. The data shown in Tables 2 and 3, and Examples 4, 5 and 8 of the specification are expression levels of cDNA rather than protein expression levels. It was known in the art that expression levels of cDNA or mRNA do not necessarily correspond to the expression level of protein since there are post-transcription regulation of mRNA and post-translational regulation of protein. Spence et al., 2006 (Molecular Cancer Research, Vol. 4, No. 1, p. 47-60) points out that "[I]n the majority of publications, total mRNA is analyzed, which does not reflect the level of translation of a given transcript. However, experiments in yeast indicate that there is little correlation between mRNA abundance and protein level". The discrepancy between mRNA and protein levels not only occurs in yeast but also in mammalian cells. Pradet-Balade et al., 2001 (Trends in Biochemical Sciences, Vol. 26, No. 4, p. 225-229)

reports that "analyses in yeast and mammalian cells have demonstrated that mRNA levels alone are unreliable indicators of the corresponding protein abundances. This discrepancy between mRNA and protein levels argues for the relevance of additional control mechanisms besides transcription" (e.g. abstract). "mRNA abundance is a poor indicator of the level of the corresponding protein … this disparity between protein and transcript levels might lead to misinterpretation of mRNA profiling results" (e.g. p. 225, right column). Anderson et al., 1997 (Electrophoresis, Vol. 18, p. 533-537) analyzed human liver by quantitative two-dimensional electrophoresis and by Transcript Image methodology, and shows a correlation coefficient of 0.48 between the mRNA and protein abundances which suggests that post-transcriptional regulation of gene expression is a frequent phenomenon in higher organisms (e.g. abstract). Fu et al., 1996 (The EMBO Journal, Vol. 15, No. 16, pp. 4392-4401) examined the regulation of p53 gene expression in human leukemmic blasts and found that there is no correlation between the level of p53 mRNA and the level of p53 protein expression in blast cells, and two cell lines having similar levels of p53 protein expression show different levels of p53 mRNA (e.g. abstract).

Further, Hanash et al., 2002 (Briefings in Functional Genomics and Proteomics, Vol. 1, No. 1, p. 10-22) points out that "[e]xpression levels of a protein depend not only on transcription rates of the gene but also on additional mechanisms, including translational regulation" and "modulation of the initiation rate of protein synthesis can influence both the overall rate of protein synthesis as well as the relative rates of synthesis of different proteins translated from different mRNA species which vary over a 100-fold range in their translation efficiency … translation of some mRNAs is increased dramatically (up to 30-fold) while overall translational

upregulation is modest (1.5- to two-fold)" (p. 14, right column). "The selective translational control can be dependent on mechanisms that target ligands to individual mRNAs, and on the differential sensitivity of mRNAs to subtle changes in the activity of components of the translation machinery" (e.g. p. 15, left column, 1st paragraph). Hanash reports that "there was a poor correlation between mRNA and protein levels, which was even weaker in tumour cell lines" (e.g. p. 15, right column, 1st paragraph). It is apparent that mRNA level does not necessarily reflect protein level.

The specification also fails to provide adequate guidance and evidence for whether the expression levels of cDNA or mRNA of PODXL gene at different differentiated stages of the hES cells could be translated into expression levels of PODXL protein. The cited Hara reference in the IDS filed 7-2-07 fails to disclose the correlation between the mRNA expression level and the protein expression level of PODXL. Hara reference discloses that PCLP1 mRNA is detected in kidney, heart, lung, brain, and muscle, but not in spleen, thymus, small intestine, or liver of adult mice (e.g. bridging p. 568 and 569). Hara shows PCLP1 protein expression in aorta-gonad-mesonephros (AGM) endothelial-like cells by immunostaining with anti-PCLP1 antibody (e.g. p. 569, right column). Expression of PCLP1 mRNA in kidney, heart, lung, brain, and muscle of adult mice does not correlate to expression of PCLP1 protein in AGM endothelial-like cells. Detection of PCLP1 mRNA in adult mice and PCLP1 protein expression in AGM region of a mouse embryo does NOT correlate mRNA level and protein level of PCLP1. The comparison of mRNAs and protein levels of PODXL (PCLP-1) has to be carried out at the same cell type or same location. The correlation between mRNA level and protein level varies depending on the tissues or cell lines analyzed. Frentzel et al., 1993 (Eur. J. Biochem., Vol. 216, p. 119-126)

analyzes proteasome protein subunit, the mouse beta-type subunit LMP2 and LMP7 (LMP, low-molecular-mass protein) and shows that "[t]he proportion of LMP2-subunit-containing and LMP7-subunit-containing proteasome complexes, as well as LMP2 and LMP7 mRNA levels, vary strongly and are shown to be dependent on the tissues or cell lines analyzed. Furthermore, high LMP2 and LMP7 mRNA levels do not always correlate with high protein levels, suggesting a specific translational mechanism which controls proteasome subunit synthesis" (e.g. abstract). Thus, absent specific guidance, one skilled in the art at the time of the invention would not know how to use antibody assay to assess or determine the extent of differentiation of hES cells as claimed.

Further, the phrase "a culture comprising human embryonic stem cells" reads on a tissue or organ culture comprising hES cells. The claims encompass assessing the hES cells for the presence of undifferentiated cells in a tissue or organ culture. The specification fails to provide adequate guidance and evidence for how to measure the protein level of PODXL, such as via antibody assay, in the tissue or organ culture, and whether there would be any difference in protein expression level of PODXL between undifferentiated and differentiated hES cells in said tissue or organ culture. Tissue or organ culture comprises not only human ES cells but also various other cells that interact with the human ES cells and such interaction could change the gene and protein expression of the human ES cells in said tissue or organ culture. The specification fails to provide adequate guidance and evidence that whether a decrease in PODXL protein expression level under the presence of a differentiating agent would be indicative of more undifferentiated cells in the tissue or organ culture. There is no evidence of record that shows a

decrease in PODXL protein expression level under the presence of a differentiating agent would be indicative of more undifferentiated cells in the tissue or organ culture.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Applicants argue that the Office fails to provide evidence to support the statement "the correlation of mRNA and protein expression levels in human glomerula epithelial cells can not be extrapolated into the correlation between mRNA and protein expression level in human embryonic stem cells" (remarks, p. 3). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph. Examiner cite references Spence et al., 2006; Pradet-Balade et al., 2001; Anderson et al., 1997; Fu et al., 1996, Hanash et al., 2002; and Frentzel et al., 1993, and demonstrates that expression levels of cDNA or mRNA do not necessarily correspond to the expression level of protein and the discrepancy between mRNA and protein levels not only occurs in yeast but also in mammalian cells. The correlation between mRNA level and protein level varies depending on the tissues or cell lines analyzed. Thus, absent specific guidance, one skilled in the art at the time of the invention would not know how to use antibody assay to assess or determine the extent of differentiation of hES cells as claimed.

Applicants argue that Office only cites one reference (Spence) and the Office must either cite a reference establishing the alleged difference in mammalian cells or alternatively provide sound scientific reasoning to support its allegation that the yeast data may be extrapolated to mammals (remark, p. 3-4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph and the reasons set forth above.

Applicants cite reference Hara and argue that Hara states that mRNA analysis of the spleen and thymus indicated that PCLP1 was not expressed in the adult mouse, thus confirming again a correlation between RNA expression and protein expression for murine PCLP1 (remark, p. 4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph and the reasons set forth above. The lack of mRNA expression in spleen and thymus does NOT mean that there is no mRNA expression of PCLP1 in adult mouse because PCLP1 mRNA is detected in kidney, heart, lung, brain, and muscle of adult mouse. Detection of PCLP1 mRNA in adult mice and PCLP1 protein expression in AGM region of a mouse embryo does NOT correlate mRNA level and protein level of PCLP1. The comparison of mRNAs and protein levels of PODXL (PCLP-1) has to be carried out at the same cell type or same location.

Applicants argue that Office fails to provide evidence or scientific reasoning to support the notion that tissue organ cultures comprises not only human ES cells but also various other cells, and organ cultures are typically established from post implantation embryos and thus could not possibly contain hES cells. The specification indicates that hES cells are obtained from pre-implantation, not post-implantation and by the time the embryo implants all hES cells will have differentiated into another phenotype (remark, p. 4-5). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph and the reasons set forth above.

The claims encompass assessing the hES cells for the presence of undifferentiated cells in a tissue or organ culture comprising hES cells. If the organ or tissue cultures could not possibly contain hES cells, then it is Not enabled to detect undifferentiated hES cells in said organ or tissue cultures. Tissue or organ culture comprises not only human ES cells but also various other cells that interact with the human ES cells and such interaction could change the gene and protein expression of the human ES cells in said tissue or organ culture. The specification fails to provide adequate guidance and evidence that whether a decrease in PODXL protein expression level under the presence of a differentiating agent would be indicative of more undifferentiated cells in the tissue or organ culture.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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